Dermatologic Applications of *Polypodium leucotomos*: A Literature Review

ABSTRACT

BACKGROUND: *Polypodium leucotomos* (PL) is a natural extract from tropical fern leaves with antioxidant and anti-inflammatory properties. It has been implicated as a potential treatment agent in multiple dermatologic conditions. **OBJECTIVE:** Here, we review the mechanism of action and current dermatologic applications of PL and extrapolate potential future dermatologic applications of PL. **DESIGN:** An extensive literature review on Pubmed was conducted in search of relevant background information and human studies utilizing PL for the treatment of dermatologic conditions. **METHODS:** Using the PubMed database, a literature search was conducted to identify relevant publications. "*Polypodium leucotomos*" was input as the key search criterion. The results were filtered by species (human) and language (English). Only papers with dermatologic applications were selected. Additionally, relevant publications found in the reference sections of selected articles were manually searched and selected. Included articles explore the origin, basic science mechanism, and various dermatologic applications of PL studied in humans. Each article was thoroughly studied by all authors and applicable data from each was used for the compilation of this review article. **RESULTS:** See Table 1 for a summary of dermatologic applications of PL based on available human clinical studies. **LIMITATIONS:** There was a limited number of human studies concerning the use of PL for treatment of dermatologic conditions and, of the available studies, many were of a small sample size. **CONCLUSION:** PL has a clinically significant role for the treatment and prevention of certain dermatologic conditions including: photoprotection, photocarcinogenesis, photoaging, vitiligo, melasma, and polymorphic light eruption. There is supporting evidence for its use in malignant melanoma high-risk patients, for enhanced actinic keratosis clearance following photodynamic therapy, and for symptomatic relief in atopic dermatitis. Potential clinical uses that require additional human clinical studies include solar urticaria, post-inflammatory hyperpigmentation, cutaneous lupus erythematosus, and other photosensitive cutaneous disorders.

KEYWORDS: *Polypodium leucotomos*, PL, antioxidant, cutaneous, photoprotection, photocarcinogenesis, photoaging, vitiligo, melasma, post-inflammatory hyperpigmentation, polymorphic light eruption, actinic keratosis, malignant melanoma, idiopathic photodermatoses, cutaneous lupuserythematosus, cutaneous porphyria

by KELLY SEGARS, DO; VICTORIA MCCARVER, DO; and RICHARD A. MILLER, DO

Dr. Segars is with the Nova Southeastern University: College of Osteopathic Medicine and Largo Medical Center Department of Dermatology in Largo, Florida. Drs. McCarver and Miller are with HCA Healthcare/USF Morsani College of Medicine at Largo Medical Center in Largo, Florida.

J Clin Aesthet Dermatol. 2021;14(2):50–60.

Origin and discovery of *Polypodium leucotomos*. *Polypodium leucotomos* (PL) is a fern with origins in Central and South America where it has a historical role in traditional medicine.[1,2] PL belongs to the Polypodiaceae family, genus *Phlebodium*.[3] Locally known as "calaguala" in reference to the species and "anapsos" when referring to the extracts,[1] PL was traditionally used for treatment of the inflammatory skin disorders, psoriasis and atopic dermatitis.[3] Additionally, its anti-carcinogenic effect has been alluded to for over 50 years.[1] PL has demonstrated the ability to lessen the harmful cutaneous effects of solar radiation with action in ultraviolet, infrared, and visible light spectra 3 in multiple *in vitro* and *in vivo* human and animal studies. Its photoprotective properties make it an attractive substance to potentially utilize, not only for the prevention of cutaneous phototoxicity, but also for the prevention and treatment of other photosensitive cutaneous conditions. There are several commercially available brands of PL in the United States and Europe, including Heliocare and Fernblock. [4]

Chemical composition of *Polypodium leucotomos*. The extract produced from the leaves of the fern, *Polypodium leucotomos*, or PL/PLE, has a chemical composition supporting its photoprotective role. It is made of phenolic compounds (benzoates and cinnamates) together with biological acid molecules (quinic, shikimic, glucuronic, and malic acids). The most abundant are 4-hydroxycinnamic acid (p-coumaric), 3-methoxy-4-hydroxycinnamic acid (ferulic), 3-dihidroxycinnamic acid (caffeic), 3-methoxy-4-hydroxybenzoic acid (vanillic), and 3 caffeoliquinic acid (chlorogenic).[5] This high phenolic content is the basis of the strong antioxidant activity observed with PL usage. For example, caffeic acid inhibits ultraviolet (UV)-induced peroxide and nitric oxide formation, while ferulic acid absorbs UV photons 6. Essentially, both acids prevent peroxidation mediated by ultraviolet radiation (UVR),[5,6] therefore, reducing deleterious generation of reactive oxygen species (ROS).

Pharmacodynamics: mechanism of action of *Polypodium leucotomos*. PL exerts vast biological effects within the human biome, of which not all are relevant to its dermatologic benefits. Here, the mechanisms of action (MOA) with downstream cutaneous effects are reviewed. In order for the reader to better understand the basic science behind PL's beneficial cutaneous effect, the negative cutaneous effects caused by solar radiation within ultraviolet (UV), infrared (IR), and visible (VIS) light spectra are explained first.

I. Solar radiation and the downstream cutaneous effects. Solar radiation is a human carcinogen ubiquitous in the environment that is responsible for many cutaneous malignancies or skin cancers. Recent data

FUNDING: This study was funded by Topix Pharmaceuticals Inc.
DISCLOSURES: The authors have no conflicts of interest relevant to the content of this article.
CORRESPONDENCE: Kelly Segars, DO; Email: Kelly.segars@gmail.com

suggests skin cancer accounts for at least 40 percent of all human malignancies.[3] It is also a major cause of photoaging.[3,7] While UV light is the most notable offender, recent studies give validity to the role of IR and VIS light in photocarcinogenesis and photoaging as well.

UVR (200–400nm) is subdivided into three categories: UVA (315–400nm), UVB (280–315nm), and UVC (100–280nm). UVC is considered negligible as it is completely filtered by the ozone. UVA is subsequently divided into two subcategories, UVA1 (340–400nm) and UVA2 (315–340nm), due to the similarity in effects of the shorter spectrum, UVA2, to UVB 8. UVR results in many downstream cutaneous effects via multiple molecular pathways.

Acute cutaneous effects of UVR are explored in depth by Jansen et al[8] and include: erythema or "sunburn," immediate pigment darkening (IPD), persistent pigment darkening (PPD), delayed tanning, epidermal hyperplasia, free radical formation, and vitamin D synthesis. Erythema is primarily caused by exposure to UVB. Sunburn after UVB exposure peaks after 6 to 24 hours. High-dose UVA2 can also result in an "immediate erythema reaction" lasting 48 to 72 hours post-exposure. IPD is caused by UVA light and is described as being gray in color and as developing minutes after irradiation and disappearing within hours. High-dose UVA, considered >10 J/cm^2, causes PPD. This is characterized by a brownish color and has a timeline that begins two hours post-exposure and lasts up to 24 hours. The phenomenae of IPD and PPD are caused by photooxidation and a redistribution of epidermal melanin, not synthesis of new melanin. Delayed tanning, caused by UVA and UVB, has a timeline that begins three days post-exposure and remains for many weeks. The cause is an actual increase in melanin synthesis due to increased tyrosinase activity. Epidermal hyperplasia, primarily induced by UVB, is a protective phenomenon that limits damage from further UVR exposure and can last up to one month. Free radical formation occurs after UV exposure in the form of reactive oxygen species: singlet oxygen, hydrogen peroxide, and superoxide radicals. These are thought to be a major consequence of UVA and result in deleterious acute effects that include damage to DNA, proteins, and cell membranes. Lastly, UVB, specifically wavelength 300 +/- 5nm, serves to convert the epidermal precursor of vitamin D into cholecalciferol.[8]

Chronic exposure to UVA and UVB can cause cancer, photoaging, and exacerbation of photodermatoses via reactive oxygen species (ROS) or free radical generation, DNA damage, immunosuppression inflammation, and abnormal remodeling of the extracellular membrane (ECM) and angiogenesis.[3,5,8.]

ROS generation, or photooxidative stress, is the principal contributor to premature aging, otherwise known as photoaging, and has implications in oncogenesis as well. UVR generated ROS results in two main actions on the cell. First, it activates cell cycle pathways, mainly mitogen-activated protein kinases (MAPK), resulting in downstream action influenced by the activator protein 1 (AP-1) and nuclear factor (NF) -κβ. These are important pathways in cell proliferation, cell death, and cell survival. Second, lipid peroxidation of cell membranes releases arachidonic acid, beginning a cascade that results in increased expression of cyclooxygenase-2 (COX-2) and resultant prostaglandin E2 (PGE2) formation. This increase in prostaglandin causes amplification of the inflammatory response.[3] Chronic sun exposure results in a deterioration of the cell's integrity and in its ability to function, ultimately, resulting in a process of photoaging, oncogenesis, and immunosuppression.[5]

DNA photodamage induced by UVR results in three main complications that have the potential to induce photocarcinogenesis. The first complication is the direct damage that occurs when certain components of DNA, known as chromophores, absorb UVB wavelengths. Chromophores are purine and pyrimidine DNA bases.[8] UVB stimulates formation of cyclobutane-pyrimidine dimers (thymine-thymine) and pyrimidine-pyrimidine dimers. These dimers down-regulate the tumor suppressor gene, p53, making cells resistant to apoptosis and able to enter mitosis without adequate DNA repair.[3,6] Secondly, indirect DNA photodamage (mainly UVA) via ROS formation promotes generation of 8-hydroxy-2'-deoxyguanosine (8-OH-dG), which is a cell marker of oxidative damage. Lastly, UVR (mainly UVA) exposure can result in damage to mitochondrial DNA (mtDNA), known as the mtDNA "common deletion." The common deletion further amplifies ROS production and decreases the cell's ability to create energy.[3] As a whole, these intermediate compounds and subsequent mutations act as early precursors of mutagenesis and cutaneous tumor formation in addition to acting as building blocks in the process of photoaging.[5]

Inflammation in relation to UV exposure is multifactorial. The cutaneous erythema reaction that occurs after UVR exposure is due to an increase in blood flow produced by the vasodilation caused by prostaglandins and nitric oxide.[5] For example, photooxidation results in NF-kB upregulation. This upregulation causes increased COX-2 and PGE2 production, which contribute to the earliest stages of inflammation. Additionally, ROS peroxidation induces activation of isoforms of nitric oxide synthase (iNOS), which mediate VEGF-induced angiogenesis and vessel hyperpermeability. Selective cell recruitment of langerhans, mast cells, neutrophils, and macrophages into the epidermis, plus an increase in pro-inflammatory cytokines IL-6 and TNF-α, also contribute to UV-induced inflammation.[35] The long term effects of UV-induced inflammation are photoaging and cancer, while the short term effects include sunburn, pain, and pruritus.[5]

Cutaneous immunosuppression after exposure to UVR is supported by noted suppression of cell-mediated immunity (Th1), a decrease in epidermal Langerhans cell presence, an increase in the production of suppressor T cells, and an altered cutaneous cytokine profile that includes an increased presence of TNF-a and IL-10.[8] The proposed etiologic mechanism of this immunosuppression is the isomerization of urocanic acid (UCA) from the trans to the cis isomer. Trans-UCA (t-UCA) originates from histidine deamination and has a biologic role in natural photoprotection via photon absorption that yields its conformational change to the cis isomer.[5] This conformational change converts UVR into a signal that is able to be identified by the immune system and activates immunosuppression.[3] Additionally, when there is a high concentration of epidermal cis-UCA (c-UCA), abnormal mast cell degranulation occurs via c-UCA's effects on epidermal LCs.5 Acute effects of cutaneous immunosuppression include susceptibility to infection, while chronic deleterious effects include chronic inflammatory diseases and carcinogenesis.

UVR causes damage to the extracellular matrix (ECM) via its activation of AP-1, which results in two major ECM-damaging downstream effects. First, activation of AP-1

interferes with the synthesis of Collagens 1 and 3 by blocking the effect of transforming growth factor (TGF)-β, therefore resulting in decreased levels of Collagen 1 and 3.[3,5] TGF-β normally functions to allow increases in collagen gene transcription. Additionally, UVR has specific actions on collagen: UVB irradiation decreases the stimulation of Types 1 and 5 collagen expression and UVA counteracts the stimulation of collagen Type I (COLa1). Second, UVR induced activation of AP-1 increases matrix metalloproteinases (MMPs) and decreases TIMPs, molecules that play a role in ECM homeostasis.[3] UVR also has an inhibitory effect on fibrillins of keratinocytes.[3,5]

Photocarcinogenesis is the end result of the chronic inflammation, photooxidation, DNA mutagenesis, and extracellular matrix alterations that occur with UVR.[3]

Infrared radiation (IR) is postulated to cause and enhance actinic sun damage (aging) and can be divided into three subcategories: IR-A (760nm–1400nm), IR-B (1400–3000nm), and IR-C (3000nm–1mm). To determine actual IR exposure, Lim et al,[9] took into account ground-based conditions and solar irradiance measurements instead of the satellite IR measurements due to a filter effect that decreases many bands of IRA, B, and C. This revealed certain absorption bands of water within IR-A are those that reach the earth's surface and cause cutaneous effects; we will refer to these as wIR-A. Sources of IR exposure are both artificial and natural; it is actually the largest portion of solar radiation. IR has an ability to reach the human subcutaneous tissue without causing a notable increase in the skin's surface temperature due to the filter effect discussed above. Prolonged exposure to wIR-A causes gross (erythema, reticular hyperpigmentation, telangiectasia), histological (modification of dermal fibers), and molecular (increased expression of MMPs and endopeptidases that degrade ECM components like collagen and elastin, increased angiogenesis by increased expression of VEGF) cutaneous effects.[7,9] These molecular effects are caused by the mitochondrial ROS generation that occurs with activation of MAPK and leads, ultimately, to transcription and translation of the MMP-1 gene. MMP-1 breaks down interstitial Collagen 1, 2, and 3.[7] Repeated exposure to IR-A results in coarse wrinkling (photoaging).[9]

Visible light (VIS, 400–700nm) makes up 44 percent of the sunlight at the Earth's surface. VIS has been reported to cause a temporary darkening of the skin called immediate pigment darkening (IPD) that can become a persistent darkening, known as persistent pigment darkening (PPD). Of note, the pigmentation induced by VIS typically only occurs in darker skin types (4–6) and has no ability to produce pigmentation in Type 2 skin.[9] VIS can also cause erythema, thermal damage, and free radical production (ROS) that promote indirect DNA damage in keratinocytes similar to that caused by UVR. Visible light is often given a "bystander" role in regards to cutaneous phototoxicity, but it is important to remember that many photodermatoses actually do have an action spectrum in VIS; many photoprotective agents are not effective against this spectrum.[7] Only sunscreens with optically opaque filters such as zinc oxide, titanium dioxide, and iron oxide are able to block VIS light.[7]

Infrared and visible light share many common actions on the human dermal fibroblast. Zamarron et al,[7] conducted a study that revealed that fibroblast cells with VIS and IR exposure have morphologic alterations that are indicative of cellular stress, an increase in cell proliferation (indicated by increased percentage of cells going through the S and G2/M phases of the cell cycle), and alterations in ECM-related protein expression. VIS and wIRA resulted in increased MMP-1 expression, and an increase Cathespin K (CTSK), which is a collagenolytic proteinase expressed with scarring and inflammation in the dermis. VIS and wIRA had contrasting effects on the expression of Fibrillin 1 (FBN1), a protein with effects on force bearing structural support, and Fibrillin 2 (FBN2), which is involved in elastic fiber assembly: VIS caused an increase in expression of FBN1 and FBN2, while wIRA caused a decrease in expression of both compared with control. VIS and wIRA also result in opposing expression of Elastin (ELN) with VIS causing increased expression and wIRA resulting in decreased expression of Elastin.[7]

We believe that the acute and chronic effects of solar radiation explored above strongly support the necessity of regular use of reliable and convenient photoprotective agents.

II. An overview of the MOA of Polypodium leucotomos. Histologically, PL induces a reduction of angiogenesis, photocarcinogenesis, and solar elastosis.[10] This histologic reduction in UV-induced phtotoxicity includes a visible reduction of sunburn cells and other photodamage effects that might correlate with reduced risk of skin cancer.[33] Cellularly, PL improves cell membrane integrity and elastin expression.[10]

PL has a concentration dependent direct antioxidant activity, resulting in inhibition of ROS and reactive nitrogen species (RNS) generation. Its high polyphenol content allows inhibition of lipid peroxidation, ultimately, providing increased cell membrane protection. Caffeic and ferulic acids have been shown to have the strongest activity, while vanillic has the weakest antioxidant activity. PL also acts as direct ROS scavenger against superoxide anion, hydroxyl, oxygen, and oxygen peroxide.[5] Solar irradiation has been shown to increase erythrocyte enzyme levels of GST and CAT, causing a concomitant decrease in plasma GSH concentration, indicating increased glutathione peroxidation. PL has demonstrated, *in vivo*, the ability to inhibit glutathione peroxidation in the epidermis and peripheral tissues by a measured increase in GSH/GSSG ratio. Essentially, PL inhibits oxidative damage via two separate mechanisms: (1) activation of natural antioxidant systems and (2) increased expenditure of GSH. Downstream cellular effects that result from inhibition of oxidative damage include reduction in the number of proliferating cells (increased p53 + cells) and inhibition of UVR-induced disorganization actin cytoskeleton and cell-cell adhesive contacts.[5]

PL inhibits DNA damage by preventing the increase of UV-induced cyclobutane pyrimidine dimers (CPDs) due to the increased p53+ suppressor activity, which reduces the number of 8-hydroxy-2'-deoxyguanosine-positive cells.[6] The decrease in CPDs correlates with improved function of DNA repair enzymes33. It also decreases UVA-dependent mtDNA damage, otherwise known as the "common deletion."[6] Finally, PL inhibits the accumulation of UV-induced COX2 and PGE by promotion of p53, preventing epidermal hyperplasia and loss of keratinocyte differentiation. The atypical keratinocytes that result from COX-2 are believed to correlate clinically with photodamage and possible AK/SCC.[10,33]

PL inhibits skin immunosuppression via multiple mechanisms. First, it inhibits the photoisomerization of t-UCA to c-UCA. t-UCA was described above as a UV-absorbing chromophore that acts as innate

photoprotection due to its ability to absorb photons.[1,5] However, photoisomerization induced by irradiation serves to create large quantities of c-UCA. c-UCA is a mediator of UVB induced immunosuppression: it exerts a deleterious effect on epidermal Langerhans cells and causes abnormal degranulation of mastocytes.[1,5] PL inhibition of the photoisomerization results in a dose-dependent decrease in c-UCA.[5] Second, PL has demonstrated, *in vivo*, the ability to inhibit glutathione peroxidation in the epidermis and peripheral tissues by a measured increase in GSH/GSSG ratio.[5] Lastly, enhanced epidermal Langerhans cell survival has been recorded; these cells are involved in tumor immunosurveillance.[3,33] These effects along with the anti-inflammatory effects below result in inhibition of the contact hypersensitivity response.[5]

The anti-inflammatory effects of PL are broad and occur via a multitude of molecular pathways. The net effect is an increase in cell survival and a decrease in apoptosis and cell death.[5] PL modulates key inflammatory signaling pathways via decreased production of key inflammatory mediators: it blocks the production of TNF-alpha, nitric oxide (NO), iNOS, COX2, and PGE2, and it inhibits activation of nuclear factors, NF-kb and AP-1.[1,5] COX-2 induces synthesis of PGI2, which causes vasodilation and inhibits platelet aggregation. With the addition of PL, there is an observed reduction in WBC extravasation and mast cell presence in solar irradiated areas. Also, the inhibition of apoptosis and cell death of fibroblasts and keratinocytes prevents the concomitant local inflammatory response via modulation of the Th1/Th2 response. PL induces the Th2 inflammatory response, resulting in increased IL-10, IL-12, and TGF-B. PL partially inhibits cytokine production in WBCs with the Th1 inflammatory response pattern, resulting in decreased levels of IL-2, IFN-γ, and IFN-α; PL also inhibits IL-6, which is part of the Th2 response. Marked inhibition of TNF-α and IL-6 might be responsible for the reduction in angiogenesis and prevention of LC depletion caused by sun radiation in humans.[5,6]

PL has a multitude of beneficial effects on ECM remodeling.[7] The extracellular matrix plays an important role in aging and modulation of these effects can result in protection from photoaging. Dermal fibroblasts are the major cell type in the dermis and are major contributors to maintenance of the ECM. PL has been shown to have protective capacity against human dermal fibroblasts exposed to IRA and VIS radiation, resulting in prevention of the aging effect. First, PL prevents dermal fibroblast cell death induced by both IRA and VIS light. It is hypothesized that this is due to an increased percentage of cells in the 'S' phase, allowing for repair of damaged DNA. PL has effects on many molecules in the ECM: for example, it inhibits MMPs, increases TIMPs, increases the secretion of elastin, reduces Cathespin K expression, and increases both Fibrillin 1 and Fibrillin 2 expression.[7] Matrix Metalloproteinases (MMPs) are collagenolytic enzymes that break down interstitial Collagen 1, 2, and 3, resulting in production of a substance called gelatin. The function of MMPs is to regulate cell growth, inflammation, and angiogenesis via this degradation of the ECM; however, overactivity can result in deleterious effects such as photoaging. PL inhibits MMP-1 expression in UVB or UVA exposed fibroblasts and stimulates TIMPs in UVB or UVA exposed keratinocytes. PL has a similar effect at wIRA and VIS wavelengths.[7] Cathepsins are collagenolytic proteinases involved in ECM remodeling. In the dermis, cathespins are expressed during abnormal circumstances, such as scarring and inflammation, for example, after exposure to VIS and wIRA light. This expression was prevented with PL.[7] Fibrillins 1 and 2 (FBN1 and FBN2) are components of extracellular microfibrils that have a role in elastin assembly during elastic fiber formation. PL caused an increase in expression of both FBN1 and FBN2 in UVA and wIRA exposed dermal fibroblasts and in UV exposed keratinocytes.[7] Loss of elastin is a major contributor to photoaging; this can occur either by increased degradation or decreased production. Solar elastosis is a haphazard deposit of elastic fibers indicative of cutaneous photoaging. It was found that PL promoted ELN expression in fibroblasts. While ELN expression increased with and without VIS and/or wIRA irradiation with PL, ELN expression was markedly increased with prior irradiation followed by PL treatment. This correlate's PL's inhibitory effect on keratinocyte elastase activity.[7]

Pharmacokinetics of *Polypodium leucotomos*. While additional studies on the pharmacokinetics are likely needed for *Polypodium leucotomos*, the current literature states the photoprotective dose in healthy humans is 7.5mg/kg PO or 0.1% weight/volume topically.[3] Bioavailability of PL is 70 to 100 percent after PO intake.[5] Its metabolism is via hepatic enzymes and is completed within 24h. Coumaric, phenolic, ferulic, and vanillic acids in PL undergo CYP450 metabolism and partial conjugation to glucuronic sulphate and acid yielding a plasma ½ life of 4–6h. There was no observed plasma esterase metabolism or binding to cellular proteins.[5]

Toxicity of *Polypodium leucotomos*. A recent meta-analysis, Winkelmann et al,[11,12] assessing 40 years of clinical and preclinical studies, found that oral PLE was administered at daily doses ranging from 120mg–1080mg, and two percent of patients (16/1016) reported mild gastrointestinal symptoms or pruritus. The study concluded the PL is tolerable at all doses with negligible risk of side effects. Furthermore, a human study[13,1] assessed the safety of Heliocare 240mg taken twice daily in 40 subjects based on history, physical exam, and laboratory values. Twenty subjects received Heliocare and 20 subjects received placebo. Safety assessments occurred on Day 0, 14, 28, and 56 and included vital signs, CBC, CMP, PT-PTT, and any recorded adverse events. There were no significant changes noted. Four subjects treated with PLE reported mild episodic fatigue, bloating, and headaches while one placebo-treated reported fatigue. It is notable that the placebo group had a 6x greater chance of experiencing at least one sunburn during the study (p=0.04).

DERMATOLOGIC USES

A summary of the dermatologic uses of PL and the supporting clinical studies can be found in Table 1.

Chemoprophylaxis for acute and chronic phototoxicity (skin cancer, anti-aging, sunburn). Phototoxicity is an ubiquitous concern in dermatologic care and the search for novel agents for photoprotection is ongoing. Current photoprotection guidelines include application of sunscreen, seeking shade, wearing photoprotective clothing, and using sunglasses. There are two categories of sunscreens: (1) physical sunscreens: contain zinc oxide and titanium dioxide and (2) chemical sunscreens: contain organic PABA, cinnamates, salicylates, and benzophenones. While these are well-established as effective against UV

TABLE 1. Summary of the dermatologic uses of PL and the supporting clinical studies

DERMATOLOGIC CONDITION	AUTHOR (DATE)	NUMBER OF SUBJECTS (AGE RANGE)	DOSING	PROPOSED MOA	OUTCOME ($P \leq 0.05$)
Acute chemophoto-protection (UV)	Middelkamp-Hup et al (2004)	Nine subjects (Fitzpatrick 2–3)	7.5mg/kg prior to sun exposure (480mg/d)	Antioxidant, immunoprotective, anti-inflammatory	Decrease in erythema in PL treated skin at 24 hours ($p<0.01$). Biopsy showed less sun-burned cells ($p<0.05$), less CPDs ($p<0.001$), less epidermal proliferation ($p<0.01$), and less mast cell infiltration ($p<0.05$)
	Kohli et al (2017)	22 subjects ((Fitzpatrick 1–3)	240mg one hour, 240mg two hours prior to UVB irradiation (480mg/d)		Colorimetry: decrease in relative erythema intensity ($p<0.05$) Histologic reduction UVB biomarkers ($p<0.05$)
Photoaging and skin cancer	Villa et al (2010)	10 subjects (29–54 years old)	240mg PL 8 and two hours before UVA	Antioxidant, immunoprotective, anti-inflammatory, ECM regulation	Decrease in CB by 84 percent with PL ($p=0.06$)
Actinic Keratosis (AK)	Auriemma et al (2015)	35 men with baldness and 2+ AKs	960mg/d every month; 480mg/d every five months	Immunoprotective, photoprotective	Decreased recurrence of AK following PDT treatment ($p=0.04$)
Vitiligo	Reyes et al (2006)	19 subjects	720mg/d + PUVA	Antioxidant, immunoprotective, photoprotective	More PL + PUVA patients achieved 50 percent or greater repigmentation compared with placebo + PUVA ($p<0.01$)
	Pacifico, 2009 (poster)	50 subjects with generalized vitiligo	Six months: 29 subjects PL 480mg every day + NB-UVB; 28 subjects placebo + NB-UVB		PL + NB-UVB increased repigmentation ($p<0.0005$). Time to repigmentation was 1 month (PL) versus 3 months placebo
	Middelkamp-Hup et al (2007)	50 subjects with vitiligo	250mg PO tid +NB-UVB biweekly for 25 to 26 weeks		Subjects with 80 percent attendance or more to NB-UVB + PL 50 percent repigmentation versus 19 percent placebo ($p<0.002$)
Melasma	Ahmed et al (2013)	33 Hispanic females with melasma	240mg PL tid for 12 weeks + topical SPF 55	Photoprotective	5.1 difference in melanin index ($p=0.14$). No statistical significance in MASI scores ($p=0.62$)
		33 Asian females from Singapore with melasma	480mg PL at 8 am and 1 pm for 12 weeks + topical hydroquinone and SPF 50+		mMASi and MelasQol scores reduced ($p<0.05$). Failed to find significant difference in melanin index score
		21 female subjects, aged 18 to 50, with epidermal melasma	PL 240mg PO bid + SPF 45 daily for 12 weeks		Statistically significant decrease in MASI scores in PL ($p<0.05$)
PMLE/Solar urticaria	Tanew et al (2012)	30 subjects with severe PMLE	<55kg: 720mg qd 56 to 70kg: 960mg qd >70kg: 1200mg qd	Antioxidant, photoprotective, immunoprotective	No PMLE lesions in 30 percent and 28 percent exposed to UVA and UVB, respectfully. Increase in mean number of UVA and UVB irradiations to elicit PMLE ($p=0.005$; $p=0.047$)
	Caccialanza et al (2007)	26 subjects (19 female; 9 male), ages 21 to 68, with severe PMLE	PL 480mg qd (7.5mg/kg a day)		Significant decrease ($p<0.05$)
	Caccialanza et al (2012)	53 subjects with severe PMLE; four with solar urticaria	480mg/d PO		73.68-percent improvement ($p<0.05$)
High-risk patients with MM	Aguilera et al (2013)	61 subjects	240mg every 8 hours for one day and 360mg 3 hours before MED	Photoprotection, antioxidant	Reduction of UVB-MED values ($p<0.005$)
Atopic Dermatitis	Romirez-Rosca et al (2012)	105 subjects, ages 2 to 17, with atopic dermatitis	Topical CS + age <6 years: 240mg/d 6 to 12 years: 360mg/d >12 years: 480mg/d	Antioxidant, immunoprotective	No significant decrease in CS use, but there was a significant decrease of antihistamine use ($p=0.038$)
SCLE	Breithaupt and Jacob (2012)	1 subject moderately controlled on hydroxychloroquine	240mg/d PL + hydroxychloroquine	Immunoprotective, antioxidant	Achieved near total remission
PCT	Hatch et al (2017)	1 subject with PCT on hemodialysis	240mg/d PO + hydroxychloroquine, topical CS, and mupirocin	Antioxidant, photoprotective	"Dramatic improvement"

radiation, a systemic photoprotective agent has the advantageous ability to provide uniform, prolonged, and total body surface protection.[14] Hence, there is a need for alternative photoprotective agents, such as the antioxidant *Polypodium leucotomos*. Topical sunscreens require frequent reapplication, and the dosing is often inconsistent and inadequate.[8] Oxybenzone (benzophenone-3) is a widely used UVB and UVA2 sunscreen in the United States. However, there are many reports of allergic and photoallergic contact dermatitis and concerns of environmental contamination of coral reefs.[9] PL shows promise as an agent that is both environmentally friendly and as an agent with an ability to block broad spectrum solar irradiation.[5] Some sunscreens have already begun to implement antioxidants in their formula: these include vitamin A (retinol), vitamin C (ascorbic acid), vitamin E (a-tocopherol), and a polyphenol component of green tea. These antioxidants have been shown to suppress ROS formation by an additional 1.7x for SPF 4 and 2.4x for SPF 15 and 50.[4,9] There have been a multitude of *in vitro* and *in vivo* clinical studies examining the effect of PL on acute and chronic phototoxicity.

Acute chemophotoprotection is important for both short- and long-term prevention of harmful sequelae of solar irradiation. Torricelli et al,[15] performed an *in vitro* study to evaluate the effects of topical PL on prevention of UVB-induced cell damage using Episkin, a reconstructed human epidermis. Topical application of 2mg/cm^2 PL immediately before UVB exposure resulted in a significant reduction in sunburn cells (80%), reduction p53 (80%), p21 (84%), and ki-67 (48%) positive cells, and prevented the formation of cyclopyrimidine dimers (CPD), confirming PL's photoprotective effect against acute UV damage.[15]

The beneficial effect of PL administration before UVR exposure has been demonstrated in multiple studies. In a study published in 2004 by Middelkamp-Hup et al,[16] nine subjects were exposed to gradually increasing doses of UV radiation (305–400nm) with and without PL administration at a dose of 7.5mg/kg. Cutaneous biopsies were taken and revealed significant decrease in mean erythema response at 24h ($p<0.01$), fewer sunburn cell numbers ($p<0.05$), decreased cyclobutane pyrimidine dimers ($p<0.01$), increase in proliferating epidermal cells ($p<0.001$), and decreased dermal mast cell infiltration ($p<0.05$). It was concluded that PL administration resulted in statistically significant cutaneous protection against UV irradiation.[1,17] A 2017 study by Kohli et al[18] sought to evaluate the impact of PL on acute UVB response in 22 subjects with Fitzpatrick Skin Type I to III via objective measurements of the effect on minimal erythema dose (MED) and histological changes. On Day 1, patients were irradiated with UVA1 and UVB and evaluated immediately and 24h post-irradiation. On Days 3 and 4, irradiation and evaluation were repeated after ingestion of PLE (240mg PL 2h and 1h prior to exposure). Assessments based on clinical observation and colorimetry revealed a decrease in UVB changes in 17/22 subjects and histology demonstrated a decrease in all 22. Reaching statistical significance, the colorimetry relative-erythema intensity post-PLE was eight percent lower ($p<0.05$) and the histologic biomarkers of UVB irradiation: DNA damage and apoptosis (sunburn cells, CPDs), inflammation (COX2), proliferation (Cyclin D1, Ki67, and proliferating cell nuclear antigen) were reduced as well ($p<0.05$).[18]

A well-known result of chronic phototoxicity is cutaneous carcinogenesis and photoaging. In one *in vitro* study, pretreatment of human keratinocytes with PL inhibited key factors implicated in skin carcinogenesis, including the UV-mediated increase of TNF-α, induction of NOS, and transcription of NFkβ and AP-1.[1] The process of photoaging and photocarcinogenesis in relation to UVA-induced "common deletion," could possibly be blunted with administration of PL according to RCT conducted by Villa et al in 2010.[19] This study assessed the effects of PL on common deletions associated with chronic UVA radiation in fibroblast and keratinocytes of 10 human subjects. Patients were exposed to set doses of artificial UVA light with or without pretreatment with PL. While results did not reach statistical significance, possibly due to small sample size, there was strong evidence of blunted increase in common deletion in patients treated with PL compared with those without, suggesting PL might prevent UVA-induced photodamage by preventing UVA-dependent mtDNA damage.[1,19] Molecular evidence has shown that wIRA and VIS light spectra also contribute to photoaging and in vitro studies using human dermal fibroblasts revealed that PL prevents these changes associated with cutaneous photoaging.[7]

Vitiligo. Vitiligo is a complex autoimmune disorder characterized by sharply demarcated hypopigmented patches of skin. Biopsy is required for diagnosis, which reveals an absence of epidermal melanocytes. It's postulated that oxidative stress and generation of ROS initiate the self-destruction of the melanocytes. Studies have documented altered antioxidant function in the epidermis and, in particular, a role for activated CD8+ T lymphocytes and IFNγ induced chemokine CXCL10 as key immune mediators for melanocyte destruction in patients with vitiligo.[21]

A universally effective treatment for vitiligo has not yet been discovered. The therapeutic goal in vitiligo treatment is to make the vitiligo less noticeable by restoring lost pigment or eliminating remaining pigment. PUVA therapy, psoralen-UVA 320–400nm, has been a standard vitiligo therapy for years. PUVA is postulated to work via T cell immunomodulatory effects, however, it has several adverse effects. Some of these adverse effects include severe sunburn, blistering, dark repigmentation an increased risk of skin cancer.[20,21] PUVA increases the risk of skin cancer by potentiating production of ROS and causing epidermal Langerhan cell depletion and local cutaneous immunodeficiency.[16] Narrow-band UVB is another, better-tolerated, treatment for generalized vitiligo. For localized vitiligo the 308nm excimer laser is preferred therapy; efficacy is increased with adjunctive topical agents such as corticosteroids, calcineurin inhibitors, and calcipotriol.[21]

PL has documented photoprotective and antioxidant effects that might lessen the risk of PUVA treatment. Additionally, PL has been proposed as a potential agent in vitiligo management due to its antioxidant, anti-apoptotic, immunomodulatory, and anti-inflammatory properties. Studies have found increased repigmentation of head and neck areas when used with adjuvant phototherapy.[22] PL's antioxidant effects and its inhibition of cell mediated immune responses, such as a decrease in IL-2, IFNγ and TNF-α, and an increase in IL-10, are the proposed mechanisms of action leading to repigmentation.

In one human RCT, Reyes et al[20] examined the effectiveness of PL as an adjuvant therapy of PUVA in vitiligo. This double-blind placebo controlled study included 19 healthy controls and 19 patients with generalized vitiligo

undergoing PUVA + 720mg/d PL and an additional 720mg dose before each irradiation. Repigmentation response was assessed at 12 weeks by clinical evaluation of three independent dermatologsts. Repigmentation response was graded as (1) none or minimal (<25%), (2) mild (25–50%), and (3) moderate to excellent (>50%). The study revealed significant increase in repigmentation for the PL-treated group, especially among those with >50 percent repigmentation response compared with placebo.[5,20,21]

NB-UVB is the current first-line treatment for vitiligo; its efficacy in combination with PL has been examined in recent studies. In a poster by Pacifico et al,[10,21,23] 57 patients with generalized vitiligo were treated twice weekly with PL for up to six months (29 received PL 480mg once daily and 28 NB-UVB alone). After blinded re-evaluation at the end of the study, the repigmentation rate of the combined therapy group was significantly higher (40% vs. 22%, $p<0.0005$). Additionally, of the responders, repigmentation was observed within one month with PL, while repigmentation was observed around Month 3 for phototherapy only. Middelkamp-Hup et al,[24] conducted a RCT 24 to determine if the addition of PL to narrow-band UVB (NB-UVB) would improve the rate of repigmentation in patients with vitiligo. The study took 50 subjects randomized to receive 250mg PO tid PL or placebo + NB-UVB two times a week for 25 to 26 weeks. Repigmentation in the head and neck area revealed (44% for PL vs. 27% placebo ($p=0.06$). Of note, patients that attended >80% NB-UVB sessions + PL showed increased repigmentation head and neck versus placebo: 50 percent PL versus 19 percent placebo ($p<0.002$). Repigmentation in the trunk, extremities, hands, and feet was not as successful. The effect might be more pronounced in Fitzpatrick II to III skin types, but Types IV to V were unable to be evaluated due to low patient numbers.[21,24]

In conclusion, PL has been shown to be a useful adjunct to PUVA and/or nb-uvb for treatment of vitiligo vulgaris. However, no studies examining the agent as monotherapy have been conducted.

Melasma. Melasma, a disorder of pigmentation occurring on sun-exposed areas of skin, is influenced by exposure to UV and visible lights, genetic factors and hormonal influences such as pregnancy and hormonal contraception/replacement. The darkened patches are often distributed in the central face affecting the forehead, cheeks, upper lip, nose and chin. It is most prevalent in women, Fitzpatrick Skin Types III to IV and individuals of Asian and Hispanic ethnicity.[12,21,25]

Existing treatment options are often incomplete and/or prone to recurrence and include: prevention of UVR, oral tranexamic acid, topical lightening agents, chemical peels (glycolic acid, salicylic acid, trichloroacetic acid), and intense pulsed light (IPL) and laser therapies.[21,25] The current gold standard treatment for melasma is topical hydroquinone cream and broad spectrum sunscreens.[25] The use of sunscreen should occur every two hours with an agent that contains UVA-blocking ingredients, such as zinc oxide, titanium dioxide, avobenzone ,and ecamsule.[21] Of note, hydroquinone has been associated with ochronosis and contact allergy, necessitating other effective treatment options.[12]

Beneficial effects of PLE have been demonstrated to increase the mean values of minimum pigmentary and erythema doses of subjects exposed to UVA and UVB radiation providing a basis for potential use in treatment of pigmentary disorders.[12] Human studies evaluating the effectiveness of PL as a photoprotective agent in the prevention and treatment of melasma have been performed. In a study conducted by Martin et al,[26] 21 women aged 18 to 50 years with epidermal melasma. The subjects were randomized into groups and given oral PL 240mg or placebo bid and applied SPF45 sunscreen daily for 12 weeks. Photographs were taken at 4, 8, and 12 weeks. MelasQOL (melasma-related quality of life), MASI (melasma assessment severity index), photos, and subject's self-assessment were used for results. At 12 weeks, MASI scores were 5.7 prior versus 3.3 post-treatment for PL group ($p<0.05$) and 4.7 prior versus 5.7 post-treatment for placebo. Fourty-three percent of PL group and zero percent of placebo group reported marked improvement. Fourteen percent of PL group and 17 percent placebo group reported mild improvement.[10,21,25] Ahmed et al[27] conducted a RCT with 40 hispanic female subjects with moderate to severe melasma defined by a melanin index >30 (the difference between affected skin and normal skin using narrowband reflectance specrophotometry). The subjects were given a 240mg PO dose of PL tid + SPF 55 sunscreen daily for 12 weeks. Outcome measures were determined by melanin index and MASI scores. Both groups revealed significant improvement in melanin index with 28.8-percent improvement in PL group and 18.3 percent in placebo, but this did not reach statistical significance ($p=0.14$). The MASI scores also revealed improvement in both groups and did not reach statistical significance ($p=0.62$). In this study PL was found to have no significant impact.[10,25] Lastly, Goh et al[12] carried out a study to determine the efficacy and safety of oral PLE for treatment of melasma in an Asian population. The study hypothesized that combination of PL with topical hydroquinone 4% and sunscreen (SPF50) would be more than effect than the combination of hydroquinone and sunscreen alone. The study encompassed 40 healthy adult patients (33 women) aged 25–65 years old with melasma being treated with topical 4% hydroquinone and sunscreen in singapore. The subjects were all of Fitzpatrick Skin Type III or IV. After randomization, subjects received two capsules of oral PLE 480mg or placebo twice daily. The mean baseline mMASI score for PLE group was 6.8 and for the control group was six. At conclusion of the study, marked improvement in mMASI scores were seen for both placebo (44.4%; $p<0.01$) and PLE (54.9%; $p<0.01$) groups. Of note, at each visit, the PLE group demonstrated a greater reduction in the mMASI score compared with placebo, which reached statistical significance at Day 56 ($p<0.05$). Meanwhile, 31.3 percent of the subjects in the PL group achieved 75 percent or greater improvement in mMASI score, while only 6.3 percent did in the placebo group ($p=0.07$). MelasQOL scores on Day 84 revealed statistically significant improvement in the PLE group ($p<0.05$). The study concluded that PL is a useful adjunctive for treatment of melasma.[12]

Photosensitive dermatoses (polymorphic light eruption and solar urticaria). Polymorphic light eruption (PMLE) is the most common idiopathic photodermatosis, occurring in 18 percent of Europeans.[28] PMLE is an autoimmune condition mediated by T-cells activated against a self-antigen induced by solar exposure.[28] Reactive oxygen species (ROS) are thought to play a significant role in the pathogenesis of PMLE after studies revealed a link between polymorphisms in the glutathione-S-transferase gene and increased susceptibility to PMLE.[28]

As discussed above, PL is a potent antioxidant and immunomodulator and might have beneficial effect in the treatment of PMLE and other idiopathic photodermatoses such as solar urticaria. Three human studies have been performed with encouraging results.

Tanew et al,[28] conducted a study in to investigate PL's efficacy in inhibiting the photoinduction of PMLE lesions via repetitive irradiation with artificial UVA and UVB light. Thirty-five subjects with a diagnosis of severe PMLE, non-responsive to high-potency broad spectrum sunscreen, were recruited with specific inclusion and exclusion criteria; additionally, most of the included subjects required previous prophylactic photodesensitization with nb-UVB and PUVA. The minimal erythema dose (MED) of each subject was determined so that individualized UVB doses correlating to one MED of UVB could be given before photoprovocation; the UVA irradiation dose was based on Fitzpatrick Skin Phototype (I = 60J/cm^2, II = 75J/cm^2, III = 85J/cm^2, IV = 100J/cm^2). Photoprovocation was repeated once daily (QD) on Days 1 to 4 or until the occurrence of typical PMLE lesions; if no lesions were present after four provocations, the subjects were eliminated as to only include subjects with low-thresholds for PMLE induction. On subsequent exposures on Days 1–4 the dose of UVB was increased by 20 percent, while the UVA dose was kept constant. Of the 35 enrolled patients, 30 were included, the other five did not show induction of typical lesions on UV exposure at baseline. On Day 7, all 30 subjects with a positive reaction to UVA, UVB, or both were started on a daily dose of PL (Fernblock) according to body weight (<55kg=720mg QD, 56–70kg=960mg QD, >70kg=1200mg QD) for two weeks. A second photoprovocation, identical to the first, followed on Days 21–28 at locations in the immediate vicinity to those that had been exposed to UV at baseline. All 30 patients with a positive test were sensitive to UVA requiring 2.3 mean photoprovocations, while 18/30 were also sensitive to UVB, requiring 3.1 photoprovocations to induce lesions of PMLE. These results were expected as previous studies have shown UVA as the major etiological waveband involved in eliciting PMLE lesions. Nine out of 30 (30%) UVA-sensitive and 5 out of 18 (28%) UVB-sensitive subjects had negative photoprovocation tests with the addition of PL. For the remaining subjects, the mean number of exposures required to produce PMLE lesions increased from 1.95 at baseline yielded 2.62 with PL for UVA (p=0.005) and from 2.38 at baseline yielded 2.92 with PL for UVB (p=0.047). The mean MED after two weeks of treatment with PL was also significantly increased from 67 to 102mJ/cm^2 (p =0.04). Fifteen subjects from the study, located in Brescia, continued to take PL for the entirety of the summer: 7 out of 15 (47%) did not experience additional PLE episodes and 4 of the remaining eight (27% of 15) only developed a minor rash with delayed onset, while the remaining four found little help with PL. This study concludes these results are of clinical relevance due to (1) the severity of the affected patients with documented resistance to other treatments and low-thresholds for provocation providing basis that PL would be even more effective in patients with mild-moderate disease (2) the delayed development of PLE lesions during exposure acts synergistically with photohardening during exposure to natural sunlight, increasing tolerance to PLE induction or attenuation of the rash to a tolerable level.[15,28]

Caccialanza et al,[29] performed a study to evaluate the responsiveness of subjects with PMLE and solar urticaria unresponsive to conventional therapies to oral PL. Twenty-eight subjects, 26 with PMLE and two with solar urticaria, were given 480mg PLE per day starting 15 days prior to solar exposure and continuing throughout a period of natural sunlight exposure. The subjects were not permitted to use UV protection filters or other drugs that could interfere with sunlight exposure. The results were based on patient report of usual skin manifestation occurrence and if affirmative, the relative severity and number of episodes along with subjective symptoms compared with previous years. The results were documented as normalization, clear improvement by 50 to 90 percent, slight improvement b7 10 to 50 percent and no improvement. Results attained significance with a p<0.05 and revealed 20/25 (80%) had some benefit: 36 percent slight, 13 percent clear, and 31 percent normalization. Of note, neither patient with solar urticaria showed any improvement.[1,29]

Caccialanza et al[30] completed a second, larger study with the same objective, yielding similar results: 57 total subjects, 53 with PMLE and four with solar urticaria, were given 7.5mg/kg PL bid for 15 days before solar exposure and continued during exposure. Again the use of UV protection was prohibited. The study resulted in 73.68 percent patients improving: 43.86 percent noted improvement, while 29.82 percent noted complete clearance (p<0.05).[5,30]

Based on these three human clinical studies, the authors believe PL has a potentially key role in the management of idiopathic photodermatoses, especially PMLE. The resistance of the subject pool to standard treatment further supports its potential ability to treat patients with less severe presentations. While the results of PL use in patients with solar urticaria were not favorable, this could be due to low study power and a study with more subjects might be beneficial to determine its effectiveness in this patient population.

Atopic dermatitis. Atopic dermatitis is a chronic inflammatory cutaneous disease with characteristic pruritus, xerosis, inflammation, and exudate. Common associations include other atopic diseases (allergic rhinitis and asthma), food allergies and secondary infections.[5] Current standard of care includes topical corticosteroids and non-steroidal agents such as tacrolimus and pimecrolimus +/- use of antihistamines for pruritus.

Ramirez-Bosca et al[5,31] conducted a multicenter, double-blind randomized controlled trial recently examined whether PL use in children and adolescents with atopic dermatitis leads to the reduction of use of topical corticosteroids in these patients.[5,1] The study included 105 patients aged 2 to 17 years with moderate atopic dermatitis treated with topical steroids. Patients were randomized to receive placebo or oral PLE 240-480mg per day, depending on subject age, for six months. During this time, the percentage of days that patients used topical steroids or other treatment were calculated. While no significant reduction was observed in topical steroid use, there was a secondarily observed decrease in use of oral antihistamines in the PLE group (p=0.038).[1,5,31]

Further studies concerning subjective symptom improvement in patients with atopic dermatitis would be beneficial to further elucidate PL's effect on the disease process. If PL serves to significantly reduce associated pruritus, the atopic population might see clinical benefit via (1) reduced symptomatology, (2) less intake of oral antihistamines, which can cause undesirable side effects such as sedation, and (3) reduced incidence of traumatic excoriation

of the lesions leading to quicker healing time and reduced incidence of secondary infection. Additionally, an analysis of gross and histologic lesion appearance pre- and post-treatment could be interesting due to the demonstrated anti-inflammatory effects of PL.

Photoprotection for patients at high risk for malignant melanoma. Malignant melanoma (MM) have been steadily increasing in incidence and identification of high-risk patients is critical to prognosis improvement. Factors that increase risk include genetic factors, ultraviolet radiation, and melanocytic nevi. The best established high risk locus for MM is the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene, causing 25 to 50 percent of familial MM. Other familial MM results from mutations downstream of CDKN2A, such as CDK4. Genes that confer moderate risk include variants in the melanocortin 1 receptor (MC1R) which produces variable quantities of red/yellow pheomelanin pigment that has a role in inducing oxidative cell-damage instead of the photoprotective black eumelanin. This pigment gene, along with others (OCA, TYR), are common in white population and produce the phenotypic red or blonde hair, Fitzpatrick Skin Type I, tendency for sun-induced freckling and reduced tanning response that confers a low-moderate increased MM susceptibility risk. For example, carriers of the red hair variant (RHV) have an increased risk of MM independent of skin phototype.[14] Protective measures for patients with increased susceptibility to MM are paramount and PL might provide benefit to this population based on its photoprotective effects.

Aguilera et al[14] conducted a human clinical study to (1) analyze the ability to of PL to decrease UV-induced erythema and (2) to study the interaction of subjects with MC1R polymorphisms and CDKN2A mutations with the MED before and after oral PL. The subject pool included 61 patients aged 15–76: 25 with familial and/or multiple MM, 20 with sporadic MM, and 16 with atypical mole syndrome without MM history. Each subject was phenotyped (Fitzpatrick 1–4, eye color, hair color, and nevus number/description), genotyped (via DNA blood tests for identification of CDKN2A and MC1R polymorphisms), and assigned a basal MED. All patients received 720mg of PL in three divided doses plus 360mg in a single dose 24h and 3h prior to a second MED assessment. During analysis, the study found that patients with at least one RHV had a tendency toward lower basal MED. Oral PL significantly increased the MED in all patients ($p<0.05$), with a higher post-PL MED in women compared with men ($p<0.05$). However, a potentially interesting finding that did not reach statistical significance ($p=0.06$) indicated that PL had a stronger effect on the MED of patients with familial MM compared with those with MM, even more drastic changes were seen in familial MM subjects with mutated CDKN2A and/or polymorphisms in MC1R. PL response rates were higher in patients with lower basal MEDs and dark eyes ($p<0.05$); both serve as independent positive prognostic indicators.[14]

Oral PL is beneficial in patients at high risk for MM due to its photoprotective properties ($p<0.005$). Patients with familial MM might derive increased benefit due to the presence of CDKN2A mutation and/or allelic variants of the MCR1 gene (R151C, R160W, D294H) which increase the cytotoxic effect of UVR and increase DNA damage and oxidative stress. Long-term follow up would be ideal to monitor efficacy of PL in this population.[10,14]

Actinic keratoses. Common premalignant skin lesions, known as actinic keratoses (AKs), can become bothersome and might eventually transform into invasive squamous cell carcinoma with an estimated risk of 65–97 percent. Many treatments are available for AKs including cryotherapy, topical chemotherapy, and Photodynamic therapy (PDT). PDT is considered one of the most effective treatments, however, there is concern that PDT might induce local DNA-mutagenesis and immunosuppression, leading to a recurrence of the treated AKs, resulting in treatment failure. AK clearance rate with PDT ranges from 60 to 90 percent with a recurrence rate of 20 percent at six months.[32] Prevention of this phenomenon would be optimal and it was hypothesized by Auriemma et al, 2015,[32] that PL might in fact reduce or reverse this UV-induced immunosuppression and mutagenesis.[32]

Auriemma et al,[32] conducted a human clinical study to examine PL's efficacy in terms of enhancing AK response to PDT and improving long-term clearance rates post-PDT on scalp lesions. The study included 35 bald men with at least two AKs on the scalp that underwent two PDT sessions one week apart. The subjects were divided into homogenized groups: one group began oral PLE one week after the second PDT session, while the other did not. The antioxidant, PL, was begun one week after the final PDT treatment to prevent interference with PDT's oxidative mechanism of action. Patients of both groups used an SPF50 sunscreen applied every two hours during sun exposure. At two months and six months after beginning oral PL, the bald areas were assessed. It was found that both groups had statistically significance clearance of AKs ($p<0.001$). The PL group was found to have a statistically significant increased rate of AK clearance compared with PDT alone ($p=0.04$). It was concluded that PL is a useful adjunct to PDT due to its ability to increase clearance and decrease recurrence, but that more studies would be necessary to further ensure no competing interaction occurs between the two therapies.[32,33]

It would be of clinical value to further examine the efficacy of PL in enhancing clearance and preventing recurrence of actinic keratoses after PDT as well as other therapeutic interventions including excision, topical therapies, and cryotherapy. Furthermore, the question of whether or not PL could provide additional protection to prevent recurrence of NMSCs, including SCC and BCC, is worth investigation. An animal study was reported to delay the development of SCC and AKs in mice following UVR with SCC decreasing from 87.5 to 57 percent and AKs decreasing from 85 to 25 percent following PL treatment.[10]

POTENTIAL USE IN OTHER DERMATOLOGIC DISORDERS

SCLE and other photosensitive dermatoses. PL has already shown significant benefit in the management of PMLE[29] and in reducing cutaneous phototoxicity from exposure to both UVA and UVB in human studies[17–19] and to wIRA and VIS light in *in vitro* human studies.[3] The authors conclude that these findings provide a strong foundation for PL's potential use in phototoxic or photosensitive conditions.

Solar urticaria has been minimally studied in Caccialanza's two human studies,[29,30] examining PL's effect on idiopathic photodermatoses. However, of the 2007 and 2011 study, only two and four subjects had solar urticaria, respectively. It is also important to keep in mind that these subjects were severely affected with poor clinical response to other treatments. A study of patients with solar urticaria ,with either

an increase in subject number or a decrease in disease severity, might demonstrate a beneficial role for PL in these patients.

For example, subacute cutaneous lupus erythematosus (SCLE), a photosensitive autoimmune disease might respond favorably to adjunct treatment with PL. PL's photoprotective and immunomodulatory properties can serve as postulated mechanisms of action. In an abstract from a case report by Breithaupt et al[34] new evidence was presented of a beneficial clinical effect of PL in a patient with moderately controlled subacute cutaneous lupus erythematosus on hydroxychloroquine. This patient achieved near total remission with the addition of PL to her treatment regimen, suggesting it might have future applications in photosensitizing dermatoses, including other forms of cutaneous lupus erythematosus.[34]

A second photosensitive disease that might derive benefit from use of PL for cutaneous porphyrias, such as porphyria cutanea tarda (PCT). The dermatologic manifestations of the porphyrias are secondary to oxidative stress due to the accumulation of porphyrin. Porphyrin is an endogenous photosensitizing molecule in skin with the ability to generate ROS upon exposure to 400–410nm ('Soret Band), part of the visible light spectrum. In cutaneous porphyrias, porphyrin can accumulate to abnormally high levels and cause photosensitivity.[8] The accumulation of water-soluble porphyrins in the skin causes formation of vesicles and bullae on sun-exposed skin.[35] With PL's demonstrated efficacy as a potent antioxidant and demonstrated of activity within the VIS light spectrum,[3] the authors suggest it can be of benefit in patients with dermatologic manifestations of cutaneous porphyrias. In support of this suggestion, a case study by Hatch et al[34,35] describes a patient on hemodialysis with PCT refractory to hydroxychloroquine and strict sun avoidance for nine months and to the addition of topical corticosteroids and mupirocin during months 9–12. At Month 12, the patient was given 240mg PO q AM of PL as supplemental treatment. After its addition, the patient began to experience dramatic improvement, which continued while he was taking it over the next 15 months.[35] Based on this case study, PL might be a beneficial adjunct to PCT treatment in patients on hemodialysis. It would be beneficial to conduct a large human clinical trial to better assess its efficacy in both patients on hemodialysis and on patients with intact kidney function.

Lastly, due to the demonstrated photoprotective properties of PL, the authors suggest that the addition of PL to drug regimens associated with cutaneous phototoxicity, such as doxycycline, might help prevent occurence of this adverse event. To our knowledge, no studies have been performed to assess the efficacy of PL on prevention of drug-induced phototoxicity, and I believe it a worthwhile avenue of exploration.

Post-inflammatory hyperpigmentation. Post-inflammatory hyperpigmentation (PIH) is an acquired disorder of pigmentation that occurs in cutaneous areas of trauma, inflammation, and even sun exposure due to stimulation of melanocytes and overproduction of melanin. It is more common in darker skinned individuals by conditions such as acne vulgaris, atopic dermatitis, and cutaneous infection.[21]

Current guidelines for treatment of PIH include sunscreen and sun avoidance in addition to management of the underlying etiologic condition. Nestor et al[21] brings to light a well-founded interest in the potential use of PL for treatment of PIH, but clinical studies are lacking. The inflammatory pathogenesis of PIH involves intermediates of the inflammatory COX pathway such as prostaglandin E2, leukotriene C4, leukotriene D4 and thromboxane 2, and resultant ROS generation. This proposes a potential site of action for PL due to its anti-inflammatory properties observed in in-vitro studies, including ROS scavenging and decreased cytokine and prostaglandin release.[21]

CONCLUSION

PL is a natural compound with origins in traditional medicine that the authors believe has numerous potential clinical benefits in dermatology. PL exerts a variety of photoprotective effects through modulation of pathways affected by solar radiation including antioxidant, anti-inflammatory and immunoregulatory pathways. PL's activity in these areas has been shown in both animal and human studies and includes decreasing DNA mutagenesis, preservation of cellular integrity and decreasing inflammatory enzymes, such as COX-2.[3,33] PL can be recommended to be used as a dietary supplement to protect against effects of solar exposure, including photoaging, chemoprevention, and acute phototoxicity.[33] In particular, PL might be of use in patients at high-risk for MM.[14] Additionally, PL can be used as an adjunct to treatment of melasma and vitiligo.[12,20,24,27] Based on PL's benefit in acquired disorders of hyperpigmentation, a study of its efficacy in PIH would be welcomed.[13] PL has demonstrated clinical benefit in patients with PMLE;[28–30] however, its benefit in other idiopathic photodermatoses, such as solar urticaria, is yet to be proven. The authors conclude that additional studies determining the clinical benefit of PL in atopic dermatitis and in adjuvant therapy with PDT are needed before conclusive evidence can be drawn on PL's potential use in these areas. Lastly, based on PL's mechanism of action, the authors extrapolate the potential use of PL for photosensitive dermatoses, such as cutaneous lupus erythematosus and cutaneous porphyrias. PL has proven to broadly reduce phototoxicity across UV, wIRA, and VIS spectra and has additional antioxidant, immunomodulatory, and anti-inflammatory properties that act in the absence of solar irradiation, but are amplified in its presence. This encompassing MOA, ability to provide photoprotection that extends beyond UVR, its proven efficacy in PMLE, and two promising case studies revealing efficacy of PL in a patient with SCLE and a patient with PCT, yield promising implications for its use in photosensitive dermatoses.[1–35]

Based on PL's documented safety profile[11,13] and its potential to reduce phototoxicity and potentially decrease manifestations of certain dermatologic conditions (Table 1),[1–35] the authors find it acceptable to recommend use of PL to patients in order to optimize photoprotection in conjunction with daily sunscreen use. However, due to PL/PLEs OTC designation as a dietary supplement, there are no requirements that all formulations of PL exhibit the same physiochemical properties; most studies completed in the United States used the Heliocare or PLE-hc formulation and, therefore, it is this formulation that has the best evidence-based recommendations.[33]

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